# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75405**

# CORRESPONDENCE

ANDA 75-405

AUG 31 1999

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated June 29, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Cladribine Injection, 1 mg/mL, 10 mL vial.

Reference is also made to your amendments dated May 10, and August 2, 1999.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is tentatively approved. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product) and is subject to change on the basis of new information that may come to our attention. The listed reference drug product upon which you have based your application, Leustatin Injection of R.W. Johnson Pharmaceutical Research Institute, is subject to a period of orphan drug exclusivity (ODE). Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(D) of the Act until the ODE has expired, i.e., February 26, 2000.

Because the agency is granting a tentative approval for this application, please submit an amendment at least 60-days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and/or controls data as appropriate. An amendment

should be submitted even if none of these changes were made. This submission should be clearly designated in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made.

The drug product that is the subject of this abbreviated application may not be marketed without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act. Also, until the agency issues the final approval letter, your product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list, (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to February 26, 2000, you should amend your application accordingly.

At the time you amend this application, please contact Michelle Dillahunt, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

/S/ 8/31/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-405

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

31

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated July 14, 1998 and your correspondence dated July 21, 1998.

NAME OF DRUG: Cladribine Injection, 1 mg/mL

DATE OF APPLICATION: June 29, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 30, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Denise Huie
Project Manager
(301) 827-5848

Sincerely yours,

/S/
Jerry Phillips 7/31/98
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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December 6, 1999

**Minor Amendment**
**Labeling**

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-405 / Minor Amendment
Product: Cladribine Injection, 1 mg/mL, 10 mL per vial

Dear Sir/Madame:

We wish to amend our tentatively approved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to identify any changes in the conditions under which the product was tentatively approved.

There have been no changes to the chemistry, manufacturing, controls, nor to the labeling since the time the tentative approval was granted. Bedford Laboratories™ is supplying 12 copies of the final printed vial labels, cartons, and package inserts.

We trust this meets with your approval. If you have any additional questions or concerns, I can be reached by phone at 440-232-3320, ext. 333 or by fax at 440-232-2772.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director of Regulatory Affairs
Ben Venue Laboratories, Inc.



A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

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December 16, 1999

**Minor Amendment**

ORIG AMENDMENT
N | AM

Office of Generic Drugs
Center for Drug evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA 75-405 / Minor Amendment
Product: Cladribine Injection, 1 mg/mL, 10 mL per vial

Dear Sir/Madame:

We wish to amend our tentatively approved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Minor Deficiency of December 8, 1999 after the method validation was completed.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

1.a. The term "conc" has been replaced with the term "amount". The revised method is provided in Attachment II.

1.b. The impurity calculation has been revised. Any detected known impurities in the sample will be calculated with respect to the areas of that particular known impurity standard and the appropriate concentrations, and not by area normalization. The method has been revised accordingly and is provided in Attachment II.

2. The specification for the residual solvent level has been revised to not more than ppm, to be consistent with the units expressed in the method. The revised specifications are provided in Attachment III.

3. This was the first lot of Cladribine produced at Ben Venue. The visible particulate appears to be an isolated event unique to this lot. The subject lot (0926-49-51852) was a small stability batch of approximately vials manufactured in February 1998. A total of vials were pulled by the Production Inspectors for visible particles.

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Our investigation found no root cause for the visible particle in the vial found by the FDA laboratory, however, it should have been caught during Production's 100% visible inspection. It is possible that during the inspection process, the particle was hung up on the stopper and not observed during the manual inspection. After Production's 100% inspection, the lot passed a Mil-Standard 105E Inspection by Quality Assurance with no defects found.

A review of the batch record found no manufacturing issues that could have contributed to the defect. A re-inspection of all remaining vials left in inventory found no visible particles. Moreover, during the FDA inspection, Fred Lochner (FDA district investigator) inspected 200 vials of cladribine drug product stored under refrigerated conditions and found all vials to be acceptable.

An evaluation of other products filled using the same vial/closure system during the same timeframe as Cladribine lot 926-49-51852 revealed no particulate issues or problems indicative of a system deficiency.

BVL manufactured a second batch of Cladribine in April 1999 (a different presentation, 8 ml per vial) which met all established specifications and did not exhibit an abnormal particulate level.

In conclusion, we could not determine an exact cause for the black particles. This appears to be an isolated incident in which a single known defect was missed during the manual inspection. The Production Inspection Department was made aware of this missed defect.

We trust this meets with your approval. If you have any additional questions or concerns, I can be reached by phone at 440-232-3320, ext. 333 or by fax at 440-232-2772.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director of Regulatory Affairs
Ben Venue Laboratories, Inc.

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March 23, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

AM

**RE:** **ANDA 75-405/Minor Amendment**
**Product:** **Cladribine Injection, USP; 1 mg/mL, 10 mL per vial**

not in USP, as of 3/29/99.

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Minor Deficiency of February 12, 1999. EFS

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Chemistry Deficiencies:

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B. ACKNOWLEDGEMENTS

1. Bedford Laboratories™ acknowledges that the sterility assurance review is still pending.

2. Bedford Laboratories™ acknowledges that careful attention must be paid when photocopying original documents to create readable copies.

3. The specifications given on page 723 of the application are for the Drug Product and were mistakenly titled as Shelf-Life specifications. The page has been corrected and is provided in Attachment XI

4. Bedford Laboratories™ acknowledges that a methods validation is required to support the ANDA and will be scheduled once analytical issues are resolved.

5. All deficiencies cited have been corrected. Please refer to Attachment XII for twelve copies of final printed vial labels, carton and package insert labeling for review. Also

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located in Attachment XI are annotated side-by-side comparisons of the proposed final printed package insert with the last draft package insert.

6. Bedford Laboratories™ acknowledges that a satisfactory establishment evaluation from the Office of Compliance is necessary for approval.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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505(j)(2) OK 7/29/98

June 29,1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

**RE: Abbreviated New Drug Application**
**PRODUCT: Cladribine Injection, 1 mg/mL, 10 mL vial**

Dear Sir/Madam:

In accordance with Section 505 (j) (1) of the Federal Food, Drug and Cosmetic Act, Bedford Laboratories is submitting in triplicate (an archival copy, a review copy and a field copy) an Abbreviated New Drug Application for Cladribine Injection, 1 mg/mL; 10 mL vial. Please note that the field copy has been sent directly to the FDA District Office in Cincinnati, Ohio.

The drug product subject to this application will be manufactured by Ben Venue Laboratories, Inc., located at 270 Northfield Road, Bedford, Ohio, 44146.

This abbreviated new drug application contains the information required by Section 505 (j)(2)(A)(i), (ii)(I), (iv), (v) and (vi). The application is provided in the format suggested by your office, and contains a copy of the package insert of the "listed drug" (Ortho Biotech, Leustatin® Injection.)

In accordance with Title 21 CFR 320.22 Bedford Laboratories requests a waiver of the requirement for submission of evidence demonstrating the *in vivo* bioavailability/bioequivalence for the drug product that is the subject of our application (Cladribine Injection, 1 mg/mL; 10 mL vial). The drug product is a solution intended solely for intravenous administration and it contains the active ingredient in the same concentration as in the listed drug.

Bedford Laboratories certifies that the methods used in, and the facilities and controls used for the manufacture, processing, packaging and holding of the drug product are in conformity with current Good Manufacturing Practices in accordance with Title 21 CFR 210 and 211. Ben Venue's signed statement is provided in Section IX (MANUFACTURING FACILITY) Subsection 3 (cGMP Certification).

Three copies of analytical methods which were used to test this product and an analytical method validation package are enclosed separately along with this application.

One copy of the Microbiological Validation, along with the drug product specification, stability protocol, and the package insert are enclosed separately with this application. This drug product was aseptically filled.

If the Agency has any comments or further requests or if we could be of any assistance in your review, the phone numbers for contact are (440)-232-3320, ext. 333 (direct) and (440)-439-6398 (fax).

Sincerely,
for Bedford Laboratories

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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**Response to Microbiology Deficiencies**

August 2, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT

FA

**RE:** **ANDA 75-405/Facsimile Amendment**
**Product:** **Cladribine Injection, USP; 1 mg/mL, 10 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Facsimile Deficiency of July 21, 1999.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Microbiology Deficiencies:

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A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

micro deficiencies

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B. Acknowledgements

Bedford Laboratories™ acknowledges that a satisfactory Methods Validation is needed to support the ANDA and that a study has been scheduled.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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May 10, 1999

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NDA ORIG AMENDMENT
N/AM

**RE:** **ANDA 75-405/Facsimile Amendment**
**Product:** **Cladribine Injection, USP; 1 mg/mL, 10 mL per vial**

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-405, for Cladribine Injection, 1 mg/mL, 10 mL per vial to remove the deficiencies cited in the Facsimile Deficiency of April 27, 1999.

The number associated with the response given below corresponds to the number identifying the deficiencies in the communication. Form 356H is provided in Attachment I.

A. Chemistry Deficiencies:

MAY 11 1999
OGD
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B. ACKNOWLEDGEMENTS

1. Bedford Laboratories™ acknowledges that the labeling portion of the amendment is still pending.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

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July 14, 1998

Mr. Greg Davis
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

NEW CORRESP

NC
NAT 7/21/98
Gregory S. Davis

Re: **Telephone Amendment** / 75-405
Product: **Cladribine Injection, - 1 mg/mL, 10 mL vials**

Dear Mr. Davis:

Please find enclosed the side by side comparison of the vial labels and carton labeling of the listed drug versus the proposed drug labeling requested in the telephone communication of July 14, 1998.

We trust this meets with your approval. If the Agency has any further questions or comments, we welcome direct contact at (440) 232-3320, ext. 333 or (440) 439-6398 (facsimile).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

RECEIVED
JUL 16 1998
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